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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/171,697 | 10/23/1998 | BORIS TABAKOFF | TBK-102-US | 8351 |

7590 09/14/2004

TALIVALDIS CEPURITIS
OLSON & HIERL
20 NORTH WACKER DRIVE 36TH FLOOR
CHICAGO, IL 60606

| EXAMINER | |
|---|---|
| HUANG, EVELYN MEI | |
| **ART UNIT** | **PAPER NUMBER** |
| 1625 | 12 |

DATE MAILED: 09/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/171,697 | TABAKOFF ET AL. | |
| | Examiner | Art Unit | |
| | Evelyn Huang | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11-19 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-19 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 11-19, 21-23 are pending.

2. In view of the following new grounds of rejection, the prosecution of this application is reopened.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is drawn to the method for treating a patient to prevent or ameliorate neuroexcitability disorders with the compound of claim 12 for treating withdrawal syndromes. Claim 21 is therefore improperly dependent on claim 12. Deleting the use in claim 12 or amending claim 21 as an independent claim would obviate the rejection. The rejection is applicable to claims dependent on claim 21.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-19, 21-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The 'withdrawal syndromes' as recited in instant claim 12 reaches out to as yet unidentified syndromes upon withdrawal of as yet unidentified drugs or substance of abuse, a description of which is not found in the specification.

The 'neuroexcitability disorders' treatable by an antagonist compound with affinity for both the glycine binding site of NMDA receptor and voltage dependent sodium channels reaches out to as yet unidentified neuroexcitability disorders, the description of which is not found in the specification.

The nexus between the antagonism of glycine binding site of NMDA receptor and voltage dependent sodium channels and the treatment or prevention of any or all of the neuroexcitability disorders is not adequately described in the specification.

### *Claim Rejections - 35 USC § 112*

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-19, 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for the method of using the inventive compound to treat withdrawal syndromes resulting from ethanol, barbiturates or opiates, to treat anxiety or seizures. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. ***.

a. *Nature of the invention.*

The instant invention is drawn to a 2-carboxy quinoline compound for treating withdrawal syndromes from any addictive substance and for treating a patient to prevent or

ameliorate neuroexcitability disorders. The diseases are recited on pages 14-15 of the specification.

b. *State of the prior art and the level of the skilled in the art.*

Different types of glycine/NMDA receptor antagonists are reviewed by Leeson (J. Med. Chem. 1994, 37(24):4053-4067). While the therapeutic potential has been suggested, at the time of the invention, antagonism of glycine binding site of NMDA receptor and voltage dependent sodium channels and the treatment or prevention of any or all of the neuroexcitability disorders has not been fully established. Indeed, the results of the use of a glycine/NMDA antagonist in a clinical trial in Alzheimer's disease were entirely negative (Leeson, page 4061, column 2). Furthermore, the criteria for identifying the subject susceptible to the neuroexcitability disorder have not been established to allow for the prevention of these disorders.

The level of the skilled in the glycine/NMDA receptor art is high.

c. *Predictability/unpredictability in the art.*

The high degree of unpredictability is well recognized in the NMDA receptor art. A slight modification of the compound would lead to profound changes in its biological activity as evidenced in the very different affinities for the glycine receptor exhibited by structurally similar compounds (Carling et al. J. Med. Chem. 1993, 36:3397-3408; page 3401, Table I; page 3403, Table III). One of ordinary skill in the art would have no basis to extrapolate the results of the tested compound to those with dissimilar structures, or to extend the in vitro result to in vivo situations

Although there are glycine antagonists with high affinity and selectivity, many of them lack activity in the CNS following systemic dosing because of their inability to cross the blood brain barrier (Lesson, page 4062, last paragraph), especially as in the instant, wherein the 2-carboxy is a likely detrimental feature toward having good in vivo activity (Carling, page 3397, first paragraph).

d. *Amount of guidance/working examples.*

The preparation of the example compound is limited to N, N-diphenyl-ureido-5,7-dichloro-2-carboxy-quinoline.

The procedures for assessing the binding for the glycine binding site on NMDA receptor and voltage dependent sodium channel, the effects on sodium current and othe NMDA-mediated

effects are described. The results for N, N-dipheneyl-ureido-5,7-dichloro-2-carboxy-quinoline in Figures 1-13.

e. *The breadth of the claims.*

Applicant's assertion that all the inventive compounds would have affinity for glycine binding site of NMDA receptor and voltage dependent sodium channels, and would be effective in treating withdrawal syndromes of any addictive substance (including the as yet unidentified substances), and/or in treating or preventing any neuroexcitablity disorders (including those as yet unidentified disorders), does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability, and the limited working examples (paragraphs c, d above).

f. *Amount of undue experimentation.*

Since insufficient teaching and guidance are provided by the specification (paragraphs c-d above), one of ordinary skill in the art, even with high degree of skill, would not be able to use all the compounds as claimed without undue experimentation.

## ***Allowable Subject Matter***

6. The compound of claim 12 for treating withdrawal syndromes resulting from ethanol, barbiturates or opiates is allowable subject matter.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Evelyn Huang
Primary Examiner
Art Unit 1625

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